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SYNTHESIS AND PROPERTIES OF 7-ACETYL-8-ARYL-9-CYANO-3-HYDROXY-6-METHYL-3,4-DIHYDRO-2H,8H-PYRIDO[2,1-*b*][1,3]THIAZINES

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7-Acetyl-8-aryl-2-(1-chloro-2-hydroxy-3-propyl)thio-9-cyano-6-methyl-1,4-dihydropyridines were obtained by treatment of 1,4-dihydropyridine-2(3H)-thiones with epichlorohydrin in the presence of sodium bicarbonate. When treated with NaOMe, these compounds are readily intramolecularly alkylated with formation of 7-acetyl-8-aryl-3-hydroxy-9-cyano-6-methyl-3,4-dihydro-2H,8H-pyrido[2,1-b]-[1,3]thiazines. We have studied amination of 2-(1-chloro-2-hydroxy-3-propyl)thio-1,4-dihydropyridines and acylation of 3-hydroxy-3,4-dihydro-2H,8H-pyrido[2,1-b][1,3]thiazines.

Keywords: 2-alkylthio-1,4-dihydropyridines, 1,4-dihydropyridine-2(3H)-thiones, 3,4-dihydro-2H,8H-pyrido[2,1-*b*][1,3]thiazines, epichlorohydrin, amination, acylation.

Based on our early studies of the reaction of 1,4-dihydropyridine-2(3H)-thiolates with electrophilic reagents [1-3], we used the reactions of 5-acetyl-4-aryl-3-cyano-6-methyl-1,4-dihydropyridine-2(3H)-thiones with electrophilic epichlorohydrin for synthesis of 2-(1,2-dihydroxy-3-propyl)thio-1,4-dihydropyridines, mimetics of glyceride derivatives of 1,4-dihydropyridines, and their cyclic analogs: acylated and hydrogenated pyrido[2,1-*b*][1,3]thiazines.

Although 3,4-dihydro-2H,8H-pyrido[2,1-*b*][1,3]thiazines have been poorly studied, their synthesis is of interest since the combination in one molecule of a 1,4-dihydropyridine ring (calcium antagonists, antioxidants, hepatoprotectors) and a 1,3-thiazine ring (antibiotics of the cephalosporin group) can lead to potential biologically active compounds. Antihypertensive and anti-inflammatory activities have been found in the corresponding hydrogenated pyrido[2,1-*b*][1,3]oxazines [4].

1,4-Dihydropiperidine-2(3H)-thiones **1** were obtained by two routes: thione **1a** [5] and thione **1b** by condensation of acetylacetone, an aromatic aldehyde, and 2-cyanothioacetamide; and thione **1c** [6] by reaction of 2-(3-nitrophenyl)methyleneacetylacetone with 2-cyanothioacetamide in the presence of an equimolar amount of piperidine followed by acidification.

5-Acetyl-4-aryl-2-(1-chloro-2-hydroxy-3-propyl)thio-3-cyano-6-methyl-1,4-dihydropyridines **2** were obtained in moderate yields by treatment of compound **1** with epichlorohydrin in the presence of sodium bicarbonate. When using stronger bases (KOH or NaOMe) instead of sodium bicarbonate, the 7-acetyl-8-aryl-9-cyano-3-hydroxy-6-methyl-3,4-dihydro-2H,8H-pyrido[2,1-*b*][1,3]thiazines **3** crystallize out from a complex reaction medium in 50%-59% yields. Compounds **3** were also obtained in 62-69% yields by intramolecular alkylation of compounds **2** by treatment with NaOMe at room temperature.

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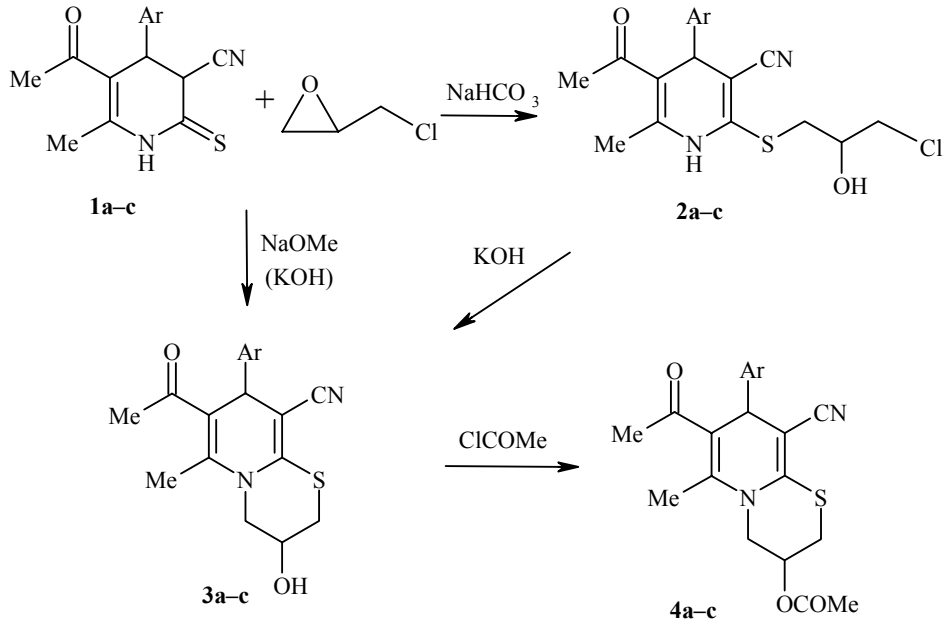
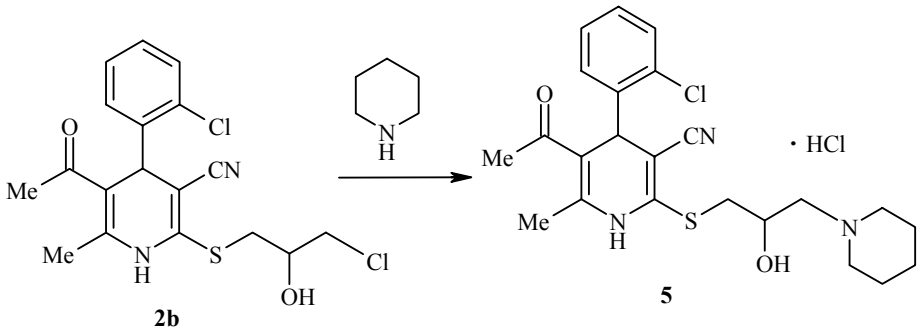


1-4 **a** Ar = Ph, **b** Ar = 2-ClC_6H_4, **c** Ar = 3-$O_2NC_6H_4$

We should note that intermolecular alkylation of 2-alkylthio-1,4-dihydropyridines at the N-1 atom occurs with significantly greater difficulty, often with transformation of the functional groups and oxidation of the ring.



When 2-(1-chloro-2-hydroxy-3-propyl)thio-1,4-dihydropyridine **2b** is treated with excess piperidine, we see formation of 2-(2-hydroxy-1-piperidyl-3-propyl)thio-1,4-dihydropyridine **5**. We should note that the presence of a 2-[1-(4-arylpiperazyl)-2-hydroxy-3-propyl]oxy group in the molecule is favorable for the formation of α_1-adrenoreceptor ligands [7, 8]. Antihypertensive properties are often exhibited by α_1-adrenoreceptor blockers. Thus combining in a single molecule 1,4-dihydropyridine groups (calcium antagonists with antihypertensive properties) [9, 10]) with potential α1-adrenoreceptor ligands may lead to new biologically active compounds.

Upon acetylation of 3-hydroxy-3,4-dihydro-2H,8H-pyrido[2,1-*b*][1,3]thiazines **3**, we obtain 3-acetoxy-3,4-dihydro-2H,8H-pyrido[2,1-*b*][1,3]thiazines **4**.

The most characteristic features of the IR spectra for compounds **1-5** are absorption bands for stretching vibrations of the cyano group, which in the case of compounds **2-5** are observed at 2188-2204 cm^{-1} and in the case of thione **1b**, at 2258 cm^{-1}. The frequencies $\nu_{C=O}$ in the case of compounds **1, 2,** and **5** decrease due to β-aminovinylcarbonyl conjugation. For compounds with a free amino group (compounds **3** and **4**), the $\nu_{C=O}$ take on values (1664-1682 cm^{-1}) typical of an acetyl group bonded to an sp^2-hybridized carbon.

In the ^{1}H NMR spectra, the most characteristic features are signals from H-4 (compounds **2** and **5**) and H-8 protons (compounds **3, 4**) at 4.66-5.38 ppm, confirming the hydrogenated structure. In the ^{1}H NMR spectra of thione **1b**, we observe *cis* and *trans* isomerism [11]. Compound **1b** is insoluble in $CDCl_3$, while in DMSO-d_6 we can determine only the *trans* isomer (δ 4.37 ppm and 4.81 ppm, J = 3.4 Hz). The signals from the *cis* isomer are strongly broadened. This means that in the case of this isomer, we observe a thione–enthiol tautomeric equilibrium [12, 13].

EXPERIMENTAL

The IR spectra of the starting compounds were recorded on a Perkin-Elmer 580B spectrometer in nujol. The ^{1}H NMR spectra were recorded on a WH 90/DC spectrometer (90 MHz), internal standard HMDS (δ 0.05 ppm). The course of the reaction and the purity of the compounds were monitored using TLC on Silufol UV-254 plates, eluent 5:5:1 dichloromethane–hexane–ethanol. The compounds were recrystallized from ethanol. The characteristics and ^{1}H NMR and IR spectral data for the synthesized compounds are shown in Tables 1 and 2.

5-Acetyl-4-(2-chlorophenyl)-3-cyano-6-methyl-1,4-dihydropyridine-2(3H)-thione (1b). A mixture of 2-chlorobenzaldehyde (2.80 g, 20 mmol), acetylacetone (2.00 g, 20 mmol) in ethanol (20 ml) and piperidine (0.5 ml, 5 mmol) was stirred for 5 min at room temperature. Then 2-cyanothioacetamide (2.00 g, 20 mmol) and piperidine (2.5 ml, 25 mmol) were added and the reaction mixture was stirred for 30 min at room temperature. Then an alcoholic solution of HCl (3 mol/l) (12 ml) was added gradually dropwise and after 20 min, the precipitate was filtered out and washed with ethanol (10 ml) (cooled down to 0°C) and water (10 ml). We obtained 4.36 g (72%) of the yellow compound **1b**; mp 159-161°C.

TABLE 1. Characteristics of Synthesized Compounds **1-5**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, % (method)
		C	H	N	S		
1b	$C_{15}H_{13}ClN_2OS$	59.15 / 59.11	4.28 / 4.30	9.20 / 9.19	10.50 / 10.52	159-161	72
2a	$C_{18}H_{19}ClN_2O_2S$	59.87 / 59.58	5.42 / 5.28	7.68 / 7.72	9.07 / 8.84	202-203	68
2b	$C_{18}H_{18}Cl_2N_2O_2S$	54.09 / 54.41	4.48 / 4.57	6.97 / 7.05	8.05 / 8.07	137-139	59
2c	$C_{18}H_{18}ClN_3O_4S$	53.09 / 53.01	4.39 / 4.45	10.16 / 10.30	7.86 / 7.59	139-141	45
3a	$C_{18}H_{18}N_2O_2S$	65.95 / 66.23	5.52 / 5.56	8.41 / 8.58	9.70 / 9.82	245-247	60 (A), 50 (B), 69 (C)
3b	$C_{18}H_{17}ClN_2O_2S$	59.70 / 59.91	4.65 / 4.75	7.73 / 7.76	8.90 / 8.89	226-228	82 (A)
3c	$C_{18}H_{17}N_3O_4S$	57.94 / 58.21	4.48 / 4.61	11.23 / 11.31	8.61 / 8.63	195-197	62 (C)
4a	$C_{20}H_{20}N_2O_3S$	64.90 / 65.20	5.48 / 5.47	7.58 / 7.60	8.83 / 8.70	182-184	64
4b	$C_{20}H_{19}ClN_2O_3S$	59.62 / 59.62	4.51 / 4.75	6.73 / 6.95	7.90 / 7.96	176-178	82
4c	$C_{20}H_{19}N_3O_5S$	57.75 / 58.10	4.39 / 4.63	10.00 / 10.16	7.71 / 7.76	199-201	78
5	$C_{23}H_{28}ClN_3O_2S\cdot HCl$	57.20 / 57.26	6.00 / 6.06	8.55 / 8.71	6.53 / 6.53	115-117	71

TABLE 2. Spectral Characteristics of Compounds **1-5**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)*
1b	1640, 1655 (C=O); 2258 (C≡N); 3250 (NH)	*cis*-isomer: 2.06 (2.1H, s, $COCH_3$); 2.37 (2.1H, s, 6-CH_3); 4.90-5.10 (0.7H, m, H-3 and H-4); 7.0-7.7 (2.8H, m, C_6H_4); 12.12 (0.7H, br. s, NH) *trans*-isomer: 2.14 (0.9H, s, $COCH_3$); 2.45 (0.9H, s, 6-CH_3); 4.37 and 4.81 (0.3H, d and d, *J* = 3.4, H-3 and H-4); 7.0-7.7 (1.2H, m, C_6H_4); 12.40 (0.3H, s, NH)
2a	1654 (C=O); 2194 (C≡N); 3128, 3240, 3274 sh. (NH, OH)	2.06 (3H, s, $COCH_3$); 2.33 (3H, s, 6-CH_3); 3.06-3.17 (2H, m, SCH_2); 3.54-3.70 (2H, m, CH_2Cl); 3.70-3.88 (1H, m, CH-OH); 4.66 (1H, s, H-4); 6.00 (1H, br. s, OH); 7.1-7.4 (5H, m, C_6H_5); 9.52 (1H, s, NH)
2b	1655 (C=O); 2196 (C≡N); 3130, 3215, 3490 (NH, OH)	2.04 (3H, s, $COCH_3$); 2.34 (3H, s, 6-CH_3); 2.88-3.20 (2H, m, SCH_2); 3.50-3.66 (2H, m, CH_2Cl); 3.88-4.27 (2H, m, CH-OH); 5.28 (1H, s, H-4); 7.10-7.50 (4H, m, C_6H_4); 8.68 and 8.74 (1H, s and s, NH)
2c	1617, 1628 sh. (C=O); 2202 (C≡N); 3152, 3252 (NH, OH)	2.16 (3H, s, $COCH_3$); 2.40 (3H, s, 6-CH_3); 3.04-3.24 (2H, m, SCH_2); 3.50-3.70 (2H, m, CH_2Cl); 4.10-4.37 (2H, m, CH-OH); 4.82 (1H, s, H-4); 7.40-8.20 (4H, m, C_6H_4); 8.82 and 8.93 (1H, s and s, NH)
3a	1682 (C=O); 2204 (C≡N); 3412 (NH, OH)	1.90 (3H, s, $COCH_3$); 2.36 (3H, s, 6-CH_3); 3.37-3.57 (4H, m and m, SCH_2 and CH_2N); 3.56-3.78 (1H, m, CH-OH); 4.80 (1H, s, H-8); 5.32 (1H, m, OH); 7.15-7.40 (5H, m, C_6H_5)
3b	1670 (C=O); 2200 (C≡N); 3418 (OH)	1.90 (3H, s, $COCH_3$); 2.34 (3H, s, 6-CH_3); 3.36-3.62 (4H, m and m, SCH_2 and CH_2N); 3.56-3.82 (1H, m, CH-OH); 5.27 (1H, s, H-8); 5.32 (1H, m, OH); 7.20-7.55 (4H, m, C_6H_4)
3c	1672 (C=O); 2195 (C≡N); 3444, 3544 (OH)	2.01 (3H, s, $COCH_3$); 2.42 (3H, s, 6-CH_3); 3.36-3.66 (4H, m and m, SCH_2 and CH_2N); 4.60-4.88 (1H, m, CH-OH); 5.08 (1H, s, H-8); 5.37 (1H, m, OH); 7.80-8.20 (4H, m, C_6H_4)
4a	1665, 1736 (C=O); 2198 (C≡N)	1.92 (3H, s, 7-$COCH_3$); 2.10 (3H, s, $OCOCH_3$); 2.40 (3H, s, 6-CH_3); 3.09-3.53 (2H, m, SCH_2); 3.96-4.42 (2H, m, CH_2N); 4.52-4.82 (1H, m, H-3); 4.68 (1H, s, H-8); 7.10-7.40 (5H, m, C_6H_5)
4b	1664, 1736 (C=O); 2194 (C≡N)	1.94 (3H, s, 7-$COCH_3$); 2.10 (3H, s, $OCOCH_3$); 2.38 (3H, s, 6-CH_3); 3.08-3.56 (2H, m, SCH_2); 3.97-4.46 (2H, m, CH_2N); 4.54-4.83 (1H, m, H-3); 5.38 (1H, s, H-8); 7.10-7.50 (4H, m, C_6H_4)
4c	1677, 1746 (C=O); 2188 (C≡N)	1.98 (3H, s, 7-$COCH_3$); 2.12 (3H, s, $OCOCH_3$); 2.44 (3H, s, 6-CH_3); 3.15-3.59 (2H, m, SCH_2); 3.97-4.43 (2H, m, CH_2N); 4.52-4.82 (1H, m, H-3); 4.85 (1H, s, H-8); 7.40-8.20 (4H, m, C_6H_4)
5	1665 (C=O); 2200 (C≡N); 3120, 3496 (NH, OH)	1.35-1.75 [6H, s, $(CH_2)_3$]; 2.02 (3H, s, CO CH_3CH_3); 2.25-2.45 [4H, m, $+N(CH_2)_2$]; 2.36 (3H, s, 6-CH_3); 2.50-2.67 (2H, m, CH_2N); 2.70-2.92 (2H, m, SCH_2); 3.70-4.10 (2H, m, CH-OH); 5.28 (1H, s, H-4); 7.4-7.5 (4H, m, C_6H_4); 9.30 (1H, s, NH)

* The ^1H NMR spectra for compounds **2a-c, 4b,c**, and **5** were taken in $CDCl_3$; the rest were taken in DMSO-d_6.

5-Acetyl-2-(1-chloro-2-hydroxy-3-propyl)-3-cyano-6-methyl-4-phenyl-1,4-dihydropyridine (2a). A mixture of 1,4-dihydropyridine-2(3H)-thione **1a** (0.54 g, 2 mmol) [4], sodium bicarbonate (0.19 g, 2.2 mmol), and epichlorohydrin (0.20 ml, 2.4 mmol) in ethanol (10 ml) was stirred for 24 h at room temperature. The sodium bicarbonate was filtered out, the filtrate was concentrated down and treated with petroleum ether. The precipitate was filtered out and washed with ethanol (cooled down to 0°C) (2 ml) and water (10 ml). We obtained 0.49 g (68%) of the colorless compound **2a** with mp 202-203°C.

Compounds 2b and **2c** (light yellow) were obtained similarly from thiones **1b** and **1c** in 59 and 45% yields.

7-Acetyl-9-cyano-3-hydroxy-6-methyl-8-phenyl-3,4-dihydro-2H,8H-pyrido[2,1-*b*][1,3]thiazine (3a). A. A mixture of compound **1a** (0.54 g, 2 mmol), a sodium methoxide solution (1 mol/l) (2 ml), and epichlorohydrin (0.20 ml, 2.4 mmol) in methanol (10 ml) was stirred for 3 h at room temperature. The precipitate was filtered out and washed with ethanol (5 ml) and water (10 ml). The filtrate was concentrated down and an additional amount of precipitate was filtered out, which was also washed with ethanol and water. We obtained 0.39 g (60%) of the yellow compound **3a**; mp 245-247°C.

Compound 3b (light yellow) was obtained similarly from thione **1b** in 82% yield.

B. A mixture of compound **1a** (0.54 g, 2 mmol), a potassium hydroxide solution (2 mol/l) in water (1 ml), and epichlorohydrin (0.20 ml, 2.4 mmol) in ethanol (4 ml) was stirred for 6 h at room temperature. The precipitate was filtered out and washed with 5 ml ethanol and water (10 ml). We obtained 0.33 g (50%) of the yellow compound **3a**; mp 245-247°C.

C. A mixture of compound **2a** (0.72 g, 2 mmol) and a sodium methoxide solution (1 mol/l) (2 ml) in methanol (10 ml) was stirred for 3 h at room temperature. The precipitate was filtered out and washed with ethanol (5 ml) and water (10 ml). We obtained 0.45 g (69%) of the yellow compound **3a**; mp 245-247°C.

Compound 3c (yellow) was obtained similarly from 1,4-dihydropyridine **2c** in 62% yield.

3-Acetoxy-7-acetyl-9-cyano-6-methyl-8-phenyl-2H,8H-pyrido[2,1-*b*][1,3]thiazine (4a). A mixture of compound **3a** (0.65 g, 2 mmol), acetyl chloride (5 ml), and potassium hydroxide (0.12 g, 2 mmol) was boiled for 3 h in a water bath. The potassium chloride was filtered out; the filtrate was concentrated down and treated with ethanol. The product was filtered out and washed with ethanol (5 ml) and water (10 ml). We obtained 0.51 g (69%) of the colorless compound **4a**; mp 182-184°C.

Compounds 4b,c (yellow) were obtained similarly in 82 and 78% yields.

5-Acetyl-3-cyano-2-(2-hydroxy-1-piperidyl-3-propyl)-6-methyl-4-phenyl-1,4-dihydropyridine hydrochloride (5). A mixture of 2-(2-hydroxy-1-chloro-3-propyl)thio-1,4-dihydropyridine (**2b**) (0.20 g, 0.5 mmol) and piperidine (0.2 ml, 2 mmol) in ethanol (3 ml) was boiled for 15 min in a water bath and stirred for 24 h at room temperature. The precipitate was filtered out and washed with ethanol (2 ml) and water (5 ml). We obtained 0.17 g (71%) of the yellow compound **5**; mp 115-117°C.

REFERENCES

1. A. Krauze, R. Verhe, and G. Duburs, *Khim. Geterotsikl. Soedin.*, 139 (1994).
2. L. Baumane, A. Krauze, L. Cernova, L. Sile, G. Duburs, and J. Stradins, *Khim. Geterotsikl. Soedin.*, 1808 (2003).
3. A. Krauze, L. Baumane, L. Sile, L. Cernova, M. Vilums, R. Vitolina, G. Duburs, and J. Stradins, *Khim. Geterotsikl. Soedin.*, 1022 (2004).
4. A. San Feliciano, E. Caballero, P. Puebla, J. A. P. Pereira, J. Gras, and C. Valenti, *Eur. J. Med. Chem.*, **27**, 527 (1992).
5. A. A. Krauze, J. E. Pelcher, Z. A. Kalme, and G. J. Duburs, *Khim. Geterotsikl. Soedin.*, 1694 (1984).
6. A. A. Krauze, R. O. Vitolina, M. R. Romanova, and G. J. Duburs, *Khim.-Farm. Zh.*, **22**, 548 (1988).
7. B. M. Khadilkar, V. R. Mestha, and S. R. Bhayade, *Indian J. Chem.*, **33B**, 451 (1994).
8. V. Cecchetti, F. Schiaffella, O. Tabarrini, and A. Fravolini, *Bioorg. Med. Chem. Lett.*, **10**, 465 (2000).
9. V. V. Kastrone, R. O. Vitolina, and G. J. Duburs, *Khim.-Farm. Zh.*, **24**, No. 6, 14 (1990).
10. N. Rojstaczer and D. J. Triggle, *Cardiovascular Drug Reviews*, **12**, 70 (1994).
11. A. A. Krauze, E. E. Liepins, J. E. Pelcher, Z. A. Kalme, and G. J. Duburs, *Khim. Geterotsikl. Soedin.*, 1504 (1984).
12. A. A. Krauze, E. E. Liepins, J. E. Pelcher, Z. A. Kalme, and G. J. Duburs, *Khim. Geterotsikl. Soedin.*, 95 (1985).
13. A. Krauze, R. Verhe, and G. Duburs, *Latv. J. Chem.*, 94 (1996).